

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

THIS PAGE BLANK (USPTO)



PCT/AU98/00519

REC'D 31 JUL 1998
WIPO PCT

Patent Office
Canberra

I, KIM MARSHALL, MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed is a true copy of the Provisional specification in connection with Application No. PO 7706 for a patent by AUSTRALIAN INSTITUTE OF MARINE SCIENCE filed on 7 July 1997.

I further certify that the annexed specification is not, as yet, open to public inspection.

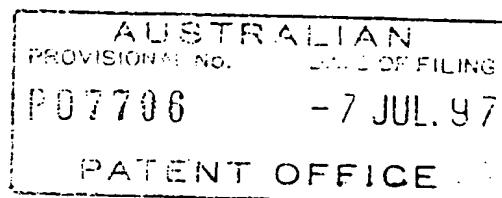
PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)



WITNESS my hand this Thirteenth
day of July 1998

KIM MARSHALL
MANAGER EXAMINATION SUPPORT AND
SALES



Australian Institute of Marine Science

A U S T R A L I A
Patents Act 1990

PROVISIONAL SPECIFICATION
for the invention entitled:

"Shaped Products or Structures for Medical or Related Purposes"

The invention is described in the following statement:

- 1A -

**"SHAPED PRODUCTS OR STRUCTURES FOR MEDICAL OR
RELATED PURPOSES"**

5

FIELD OF THE INVENTION

This invention relates to shaped products or structures for medical or related purposes, and in particular to shaped products or structures for use in bone tissue engineering in the fields of human medicine and dentistry, as well as in non-human veterinary fields.

15 **BACKGROUND OF THE INVENTION**

Crane *et al.* (1995) point out that skeletal deficiencies resulting from trauma, tumours or abnormal development frequently require surgical intervention to restore normal tissue function. Even though current surgical treatments are often successful, 20 all have associated problems with limitations. The limited supply of autograft tissue and the potential of pathogen transfer with allografts have inspired surgeons and engineers to search for other methods to repair skeletal defects. Synthetic materials such as metals and bone cements have also been used for many years, but often result in stress-shielding to the surrounding bone and fatigue failure of the implant.

25

These authors also point out that recent strategies to engineer bone have focused on the use of natural or synthetic materials as scaffolds for cell transplantation or as conduits to guide new bone growth. The success of the strategy is highly dependent on the properties of the material, requiring minimally that it be 30 biocompatible, osteoconductive, easily sterilized and degradable over an appropriate

- 2 -

time-scale into products that can be metabolized or excreted. In addition, scaffolds for cell transplantation must have a high porosity for maximal cell loading, surface characteristics that support cell growth and differentiated function and appropriate pore morphology for bone tissue ingrowth *in vivo*. The success of conduits relies on their 5 ability to induce surrounding tissue to invade, grow and replace the implanted material.

A variety of materials are under consideration for use as scaffolds or conduits in accordance with these strategies, however there remains a need for new biomaterial that will interact with living bone tissue and modulate bone formation and repair.

10

In US Patent No. 3,929,971 (Research Corporation) there is disclosed a synthetic biomaterial having a microstructure substantially corresponding to the microstructure of porous carbonate skeletal material of marine life and made up of hydroxyapatite or whitlockite. This synthetic material is made by converting porous 15 carbonate skeletal material of marine life into a phosphate skeletal material possessing a microstructure substantially the same as or corresponding to the microstructure of the carbonate skeletal source material by subjecting the carbonate skeletal material to hydrothermal chemical exchange with a phosphate.

20

US Patent No. 4,861,733 (Interpore International) discloses calcium phosphate materials useful as bone substitution material or for the manufacture of prosthetic devices which have been prepared from calcium hydroxyapatite material which has a uniformly permeable microporous structure characterised by a substantially uniform pore volume in the range from about 10 to about 90% and by a pronounced three- 25 dimensional fenestrate structure corresponding to the microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material of marine life, by reacting the calcium hydroxyapatite material which has a calcium to phosphorous atomic ratio of about 1.66 with a phosphate-contributing or phosphorous-contributing moiety or with a calcium-contributing or calcium oxide-contributing moiety so as to alter the calcium 30 to phosphorous Ca/P atomic ratio to yield a calcium phosphate material retaining the

above-described microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material but having a calcium to phosphorous Ca/P atomic ratio less than or greater than 1.6.

5 Related US Patent No. 4,976,736 (Interpore International) discloses synthetic biomaterials useful for orthopedic dental applications which have a base portion of calcium carbonate and a surface layer of a synthetic phosphate such as hydroxyapatite. The base portion may be a calcium carbonate structure having three-dimensional interconnected porosity such as may be found in porous skeletal 10 carbonate of marine life, e.g. coral porites skeletal aragonite, or it may be porous or non-porous granules of calcium carbonate.

SUMMARY OF THE INVENTION

15 According to the present invention, there is provided a shaped product or structure for medical or related purposes, characterised in that it is formed from coral of the species *Acropora*, particularly *Acropora grandis*.

The present invention also provides a device for medical or related purposes 20 which comprises an assembly of shaped products or structures, as broadly described above.

Throughout this specification, unless the context requires, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the 25 inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

DETAILED DESCRIPTION OF THE INVENTION

Coral is the hard deposit consisting principally of calcium carbonate which is built up by minute colonial marine invertebrate animals called coral polyps. The corals of the order *Hydrocoralline* of the Class *Hydrozoa* exist as sessile colonies with a massive encrusting or branching exoskeleton with pits in the surface from which the polyps arise.

The corals of the orders *Alcyonaria* and *Zoantharia* of the Class Anthozoa (Actinozoa) are of different form and habits. Those of the alcyonarians are made up of minute spicules formed within the tissues, occasionally compacted in a hard central rod running through the entire colony and sometimes supplemented by an external covering. Zoantharian corals build up hard deposits externally beneath the basal disk which attaches them to the ocean floor. As new individuals arise from the edge of the living tissue their deposits become continuous with those already laid down and so large colonies produce extensive masses of coral rock. The form of these deposits varies. Some are slender and branching and others rounded and massive. They have received common names such as staghorn coral and brain coral (Van Nostrand's Scientific Encyclopaedia, Eight Edition, Van Nostrand, Reinhold, 1995).

20

Surgical repair of large cortical and other defects, in both humans and non-humans, resulting from traumas or tumour resection presents many challenges. Significant morbidity is associated with autograft harvest sites and the quantity of material available for use in the repair is limited. A bone defect might regenerate more efficiently if a stromal substitute is implanted to provide a framework for organisation of the osteons. By providing a scaffold containing spaces morphologically compatible with osteons and their vascular interconnections, an association between biocomponents and biologic regenerative and repair responses can be promoted.

Each year, a large number of cases involved with bone fractures and deficiencies result in mechanical fixation using temporary or permanent hardware. The use of natural and biodegradable materials for surgical applications can provide strong, biocompatible and degradable hardware that can be manufactured with low cost and 5 may consequently reduce the need for a second surgical intervention following the healing process. It also can be custom fabricated according to special needs. High risk, elderly patients may represent a particular challenge since increasing the need of a second surgical intervention and hospitalization time is crucial. There is a growing search for biocompatible and biodegradable materials for use as hardware for surgical 10 applications.

A wide range of metallic, ceramic, polymeric and composite materials have been used in the construction of medical devices for implantation into the human body (Hench and Wilson, 1993). The types of implant can be presented as follows: (1) 15 nearly inert; (2) porous; (3) bioactive; (4) resorbable. Porous structure devices were developed to prevent loosening of the implants. When the porous implant is metal, the large interfacial area can provide a focus for corrosion of the implant and loss of metal ions into the tissue. A film of hydroxyapatite (HA) often coats these, for a more rapid bond of the natural bone to the devices (Hench and Wilson, 1993; Lacefield, 1993; 20 Dunn and Maxilian, 1994). The coatings, however, often dissolve with time, which limits their effectiveness. In porous implants, it is necessary for the pores to be at least 100 micrometers in diameter to allow capillaries to provide a blood supply to the ingrown connective tissue. It is important to note that interfacial stability is crucial for a clinical successful implantation. Resorbable implants are designed to gradually 25 degrade and be replaced with natural tissue, leading to regeneration of tissue instead of its replacement. The difficulty is to meet the requirements of strength and short-term and mechanical performance during the processes.

Carbonate skeletons of coral polyp and other reef-building organisms possess 30 a unique microporous lattice structure. This lattice structure promotes ingrowth of

connective tissue and eventual bone deposition within the scaffold. Each species of organism governs the microstructural properties of its skeleton to a high degree, however the morphological parameters used to describe the colonies taxonomically do not suffice to characterise them from a materials standpoint. The rationale for using 5 the calcium carbonate structure of coral as a bone substitute material is based on the fact that natural bone is approximately 70% hydroxyapatite by weight and 50% by volume. Porosity and interconnectivity are key factors with respect to the amount and type of ingrowth of tissue into the lattice structure of coral. For example, in highly porous and interconnected implants, tissue ingrowth starts by day three or four. By 10 four weeks, the ingrowth is completed and apposition of bone covering the pore walls has began. In animal models, bone ingrowth may be nearly complete by three months.

The study of coral as an osseous substitute began as early as 1970s in France 15 and USA. It reflects different ideas and approaches, the first human graft was carried out in 1979 (Patel *et al.*, 1980). One of the early approaches by American researchers was to replicate the porous calcium carbonate skeletal structure of some marine organisms (White *et al.*, 1972). They replicated the microstructure in ceramic, metal, and polymer prosthetic materials in a process that they termed replamineform (White 20 *et al.*, 1972). In another process, using hydrothermal exchange, coral skeletal carbonate was converted to calcium phosphate (Roy and Linnehan, 1974). The result was a compound with good biocompatibility and hardness, its derivatives are still a common material in bone grafting. There is however a continuous debate (Holmes, 1979; Shors and Holmes, 1993; Marchac and Sandor, 1994; Ripamonti, 1996), over 25 the properties of the converted material. It is argued that the conversion process may cause the coral to lose some of its unique properties that are characterised by its architectural configuration and integration into bone tissue. Both natural and converted coral have undergone some clinical trials and are currently available. Coralline and coralline derivative implants are also under experimental study using animal models 30 (e.g. Glass, 1989; Brain *et al.*, 1993; Ripamonti, 1996) and human clinical trials and

evaluation for repair or replacement of broken or diseased bones. Studies are currently being conducted for restoration or replacement of both broken and diseased bone for orthopaedic, cranial, maxillofacial, dental and ocular and orbital floor implants (e.g. Holmes, 1993; Papacharalambous, 1993; Bronzino, 1995; Braye *et al.*, 1996; 5 Mercier *et al.*, 1996).

It has also been suggested that in some cases of mechanical failure of internal fixation for hip fractures, which is common in elderly patients, replacement of lost bone trabeculae may improve the mechanical strength of fixation (Ciotteau, 1993). Holmes 10 (1993) has summarised the main clinical applications for porous hydroxyapatite of marine origin. In most of these cases, solid blocks, rods or granular forms of coralline materials have been used to fill gap and contour defects (Marchac and Sandor, 1994).

It has been noted that the main obstacle in the use of hydroxyapatite and 15 porous coralline materials for load-bearing implants is the relatively poor mechanical properties of these materials, mainly low elasticity and high brittleness, and suggested that future development should focus on the optimisation of properties and microstructural components of the material and impregnation with molecular and cellular agents (Holmes, 1993; Crane *et al.*, 1995; Ashby *et al.*, 1996; Dee and Bizios, 20 1996).

Acropora species grow widely throughout the tropic seas. The most common growth form of Acropora is the branched form with *Acropora grandis* forming staghorn-like colonies. Figure 1 presents a computerised illustration of a typical colony. 25 Branches can be very long (a few metres in height) and as thick as 10-15cm. This species grows 20-25cm a year. Since this species is very common and fast growing, samples can be easily collected in sheltered areas of the coral reefs. In addition it is also very easy to culture this species so that collection from the coral reefs can be avoided by use of cultured coral material.

The average skeletal density of *Acropora grandis* is ~2.7g/cm³. Because the skeleton of this coral species is dense and strong, it can be easily machined to a variety of configurations of shaped products or structures of different sizes, for example by grinding. This material is particularly suited for use in an implant device, in particular for load bearing bones where strength is an essential property of the implant device.

As previously described, the shaped products or structures of the present invention are provided for medical or related purposes. The term "medical or related purposes" is used throughout this specification to include the fields of human and non-human medicine and dentistry in particular. Thus the shaped products or structures of this invention may be used as bone implants or prostheses, or as dental implants or prostheses. In other embodiments, the shaped products or structures may be "hardware" items for medical or related purposes including, but not limited to, various cylinders, sleeves, pins, screws, bolts, nuts, spacers, flat or curved plates or the like. Some typical hardware items are shown by way of example only in Figure 2.

The present invention also extends to devices for medical or related purposes which comprise an assembly of two or more shaped products or structures of this invention. Figure 3 shows a typical such device, however it is to be understood that this Figure is included by way of example only and the present invention is not restricted to devices of the type shown in Figure 3.

Figure 3 shows an implant device 10 for insertion between the ends 30 and 31 of a long bone (see Fig 3e), for example the ends formed by fracture of the long bone, or when elongation of the bone is needed. Device 10 comprises a threaded male pin 11 (see Fig 3a), an internally threaded female socket 12 (see Fig 3b) and an internally threaded locking nut 13 (see Fig 3c). Fig 4d shows the assembled device 10. As shown in Fig 3a, male pin 11 (which is optionally hollow as shown at 23) consists of an externally threaded shank portion 21 and a head portion 22 which incorporates a

socket 24 of suitable dimensions to receive the end of a long bone, which in use of the device will be fixed into the socket, for example using bone cement or similar material or by use of suitable screws, pins or the like. Female socket 12 is internally threaded as shown at 25, and is similarly provided with a socket 26 to receive the end portion 5 of a long bone. Locking nut 13 is also internally threaded as shown at 27. It will be evident from Fig 3d which shows the assembled device 10 that the overall length of the device, and hence the distance between the ends of a long bone into which the device is inserted, can be adjusted by screwing the female socket 12 along the shank portion 21 of the male pin 11, and then locking the socket 12 in place with the locking 10 nut 13.

In work leading to the present invention, off-shore coral colonies were collected from the Great Barrier Reef using lifting bags and baskets. The colonies were immediately soaked in a bleaching solution. Since clearing the residual organic matrix 15 is one of the first tasks in the purification process, the first steps were started immediately following collection of the coral. It has been found that by bleaching the colonies immediately after collection and while the colonies were still wet, the best results and cleanest colonies were obtained.

20 The colonies were then cut into blocks (6X6X15) and machined into a variety of configurations as shown by way of example in the photographs of Figure 2 (B-H). After the initial bleaching and cleaning processes, samples were oven dried and kept in a semi-sterile, dry environment to avoid humidity and bacterial infections of the cleaned skeletal materials.

25

Special holders were fabricated from soft polyvinylchloride polymer material to firmly secure the samples to avoid fractures during the machine processing of the samples.

- 10 -

Oven dried samples were transferred into an hydrostatic pressure chamber where distilled water was pressurised (150psi) into the skeleton, and particularly the fine cavities. This process reduces the amount of dust particles produced and allows easier machining (eg. grinding) of the samples. As an alternative, it has been found 5 that dipping samples in liquid nitrogen creates a more solid substrate. After dipping in liquid nitrogen for 2 minutes, processing of the samples was easier and the surface produced by the machine processing was smoother.

As noted above, the products or structures may be machined into a variety of 10 configurations for various medical or related purposes, and quite complex shapes such as cylindrical structures and threaded structures may be formed by appropriate machine processing.

Finally, the shaped products or structures of the present invention may be used 15 to adsorb or bind, and deliver, other therapeutically active substances which assist in the bone repair or regeneration process, or which have other desired therapeutic activity. Such substances include, by way of example, known synthetic or semisynthetic antibiotics which may be introduced into the pore cavities of the shaped product or structure, or a growth factor such as transforming growth factor or one of 20 the bone morphogenic proteins which can be used to assist or promote bone ingrowth.

Persons skilled in this art will appreciate that variations and modifications may be made to the invention as broadly described herein, other than those specifically described without departing from the spirit and scope of the invention. It is to be 25 understood that this invention extends to include all such variations and modifications.

REFERENCES:

Ashby, E.R., Rudkin, G.H., Ishida, K. and Miller, T.A. (1996). Evaluation of a novel osteogenic factor, bone cell stimulating substance in a rabbit cranial defect model. *Plast. Reconstruct. Surg.*, **98**:420-426.

Brian, K. *et al.* (1993). Repair of large cortical defects with block coralline hydroxyapatite. *Bone*, **14**:225-230.

Braye, *et al.* (1996).

Bronzino, J.D. (1995). The biomedical engineering handbook. CRC Press: Boca Raton.

Cirotteau, Y. (1993). The use of biocoral for hip fracture repair in elderly patients. *In:* Allemend, D. and Cuif, J.P. (eds). Biominerization 93. 7th Inter. Symp. on Biominerization. Monaco, pp.129-134.

Crane, G.M., Ishaug, S.L. and Mikos, A.G. (1995). Bone tissue engineering. *Nat. Med.* , **1**:1322-1324.

Dee, K.C. and Bizios, R. (1996). Mini-review: Proactive biomaterials and bone tissue engineering. *Biotech. Bioeng.*, **50**:438-442.

Dunn, M.G. and Maxian, S.H. (1994). Biomaterials used in orthopaedic surgery. *In:* Greco, R.S. (ed). Implantation biology: The host response and biomedical devices. CRC: Boca Raton, pp.230-252.

Glass, A.D., Mellonig, J.T. and Towelt, H.J. 91989). Histologic evaluation of bone inductive proteins complexed with coralline hydroxyapatite in an extra skeletal site of the rat. *J. of Per. Onto.* , **60**:121-126.

Hench, L.L. and Wilson, J. (1993). An introduction to bioceramics. *In:* Hench, L.L. and Wilson, J. (eds). An introduction to bioceramics. World Scientific Press. pp.1-24.

Holmes, R.E. (1979). Bone regeneration within a coralline hydroxyapatite implant. *Plastic and Reconstructive Surgery*, **63**:626-633.

Lacefield, R.W. (1993). Hydroxyapatite coating. *In:* Hench, L.L. and Wilson, J. (eds). An introduction to bioceramics. World Scientific Press, pp 223-238.

Marchac, D. and Sandor, G. (1994). Use of coral granules in the craniofacial skeleton. *J. of Craniofacial Surg.*, **5**:213-217.

- 12 -

Mercier, *et al.* (1996). The coral orbital floor. *Rev. Stomatol. Chir. Maxillofac.*, 6:324-331.

Papacharalambous, K.S. and Anastasoff, K.I. (1993). Natural coral skeleton used as onlay graft for contour augmentation of the face. *Int. J. Oral. Maxillofac. Surg.*, 22:260-264.

Patel, H., Onnard, F., Gullemin, G., and Patat, J.L. (1980). Utilisation de fragment de coraux madreporeux en chirurgie orthopédique et réparatrice. *Chirurgie*, 106:199-205.

Ripamonti, U. (1996). Osteoinduction in porous hydroxyapatite implanted in heterotopic sites of different animal models. *Biomaterials*, 17:31-35.

Roy, D.M. and Linnehan, S.K. (1984). Hydroxyapatite from coral skeletal carbonate by hydrothermal exchange. *Nature*, 247:220-222.

Shors, E.C. and Holmes, R.E. (1993). Porous hydroxyapatite. In: Hench, L.L. and Wilson, J. (eds). An introduction to bioceramics. World Scientific Press, pp. 181-198.

White, R.A., Weber, J.N. and White, E.W. (1972). Replamineform: A new process for preparing porous ceramic, metal, and polymer prosthetic materials. *Science*, 176:922-924.

Dated this 7th day of July, 1997

Australian Institute of Marine Science

By its Patent Attorneys

Davies Collison Cave

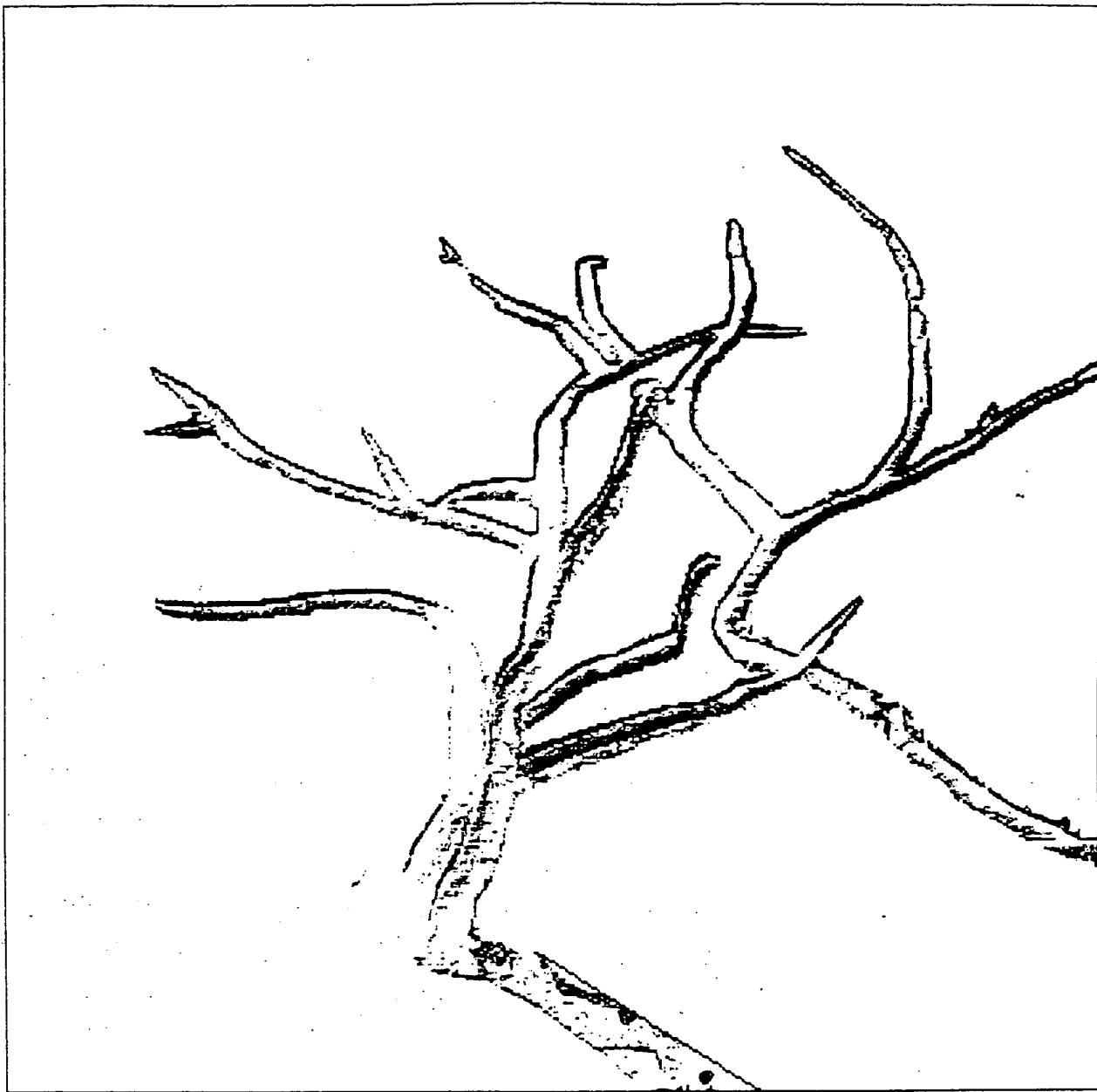


FIGURE 1

B

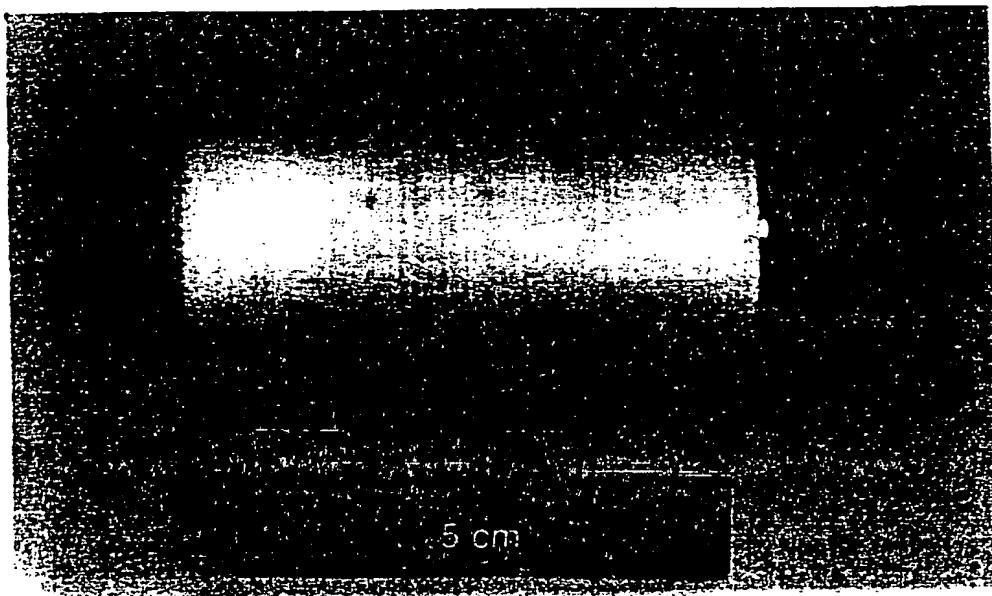
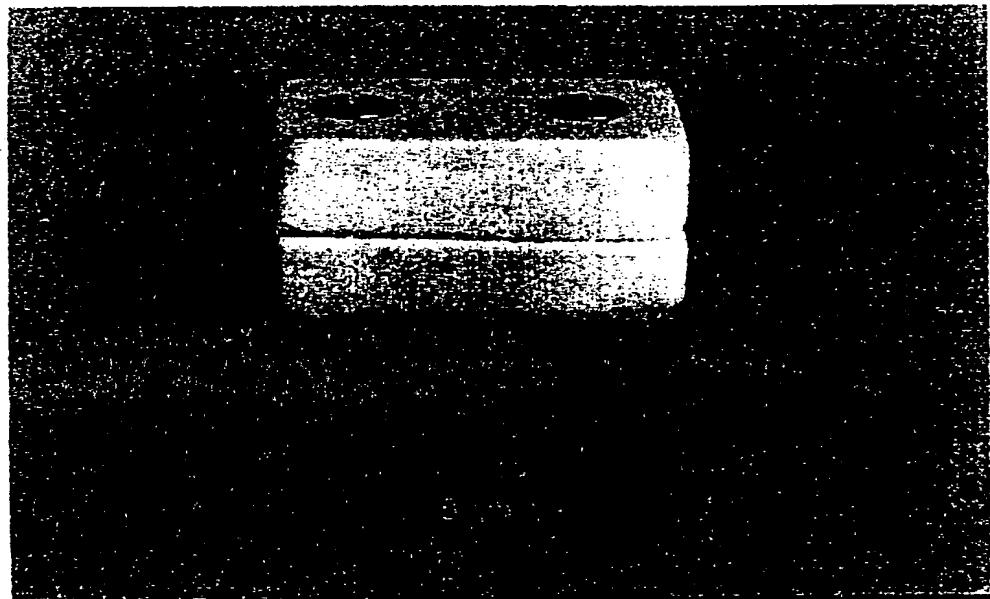
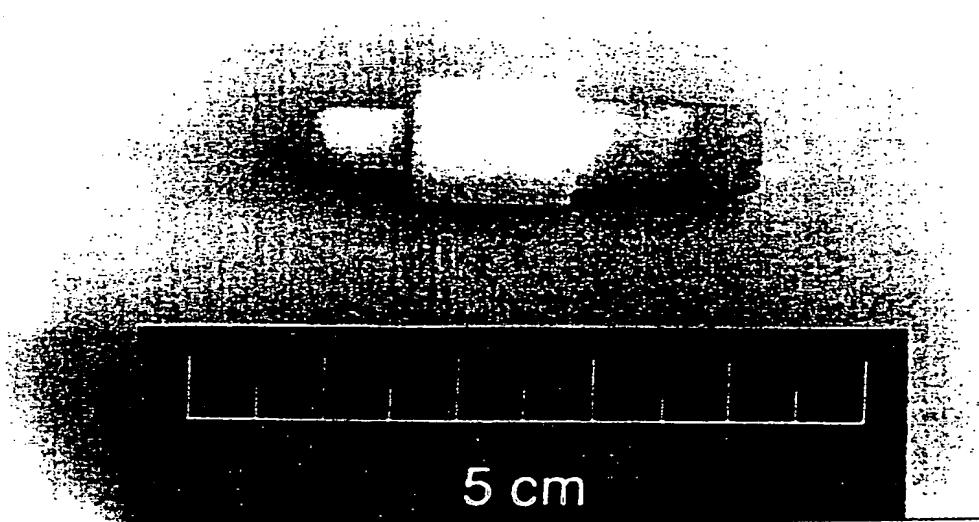


FIGURE 2

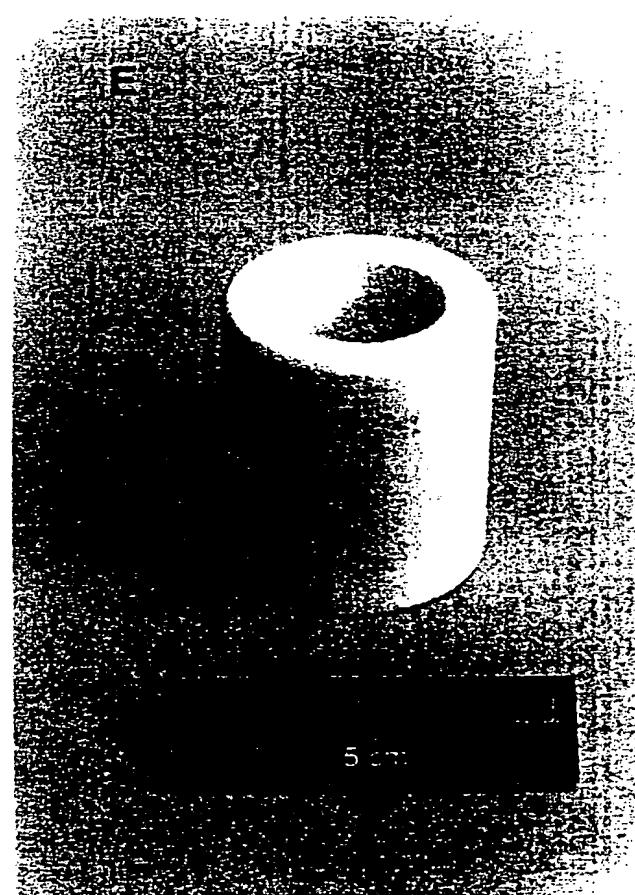
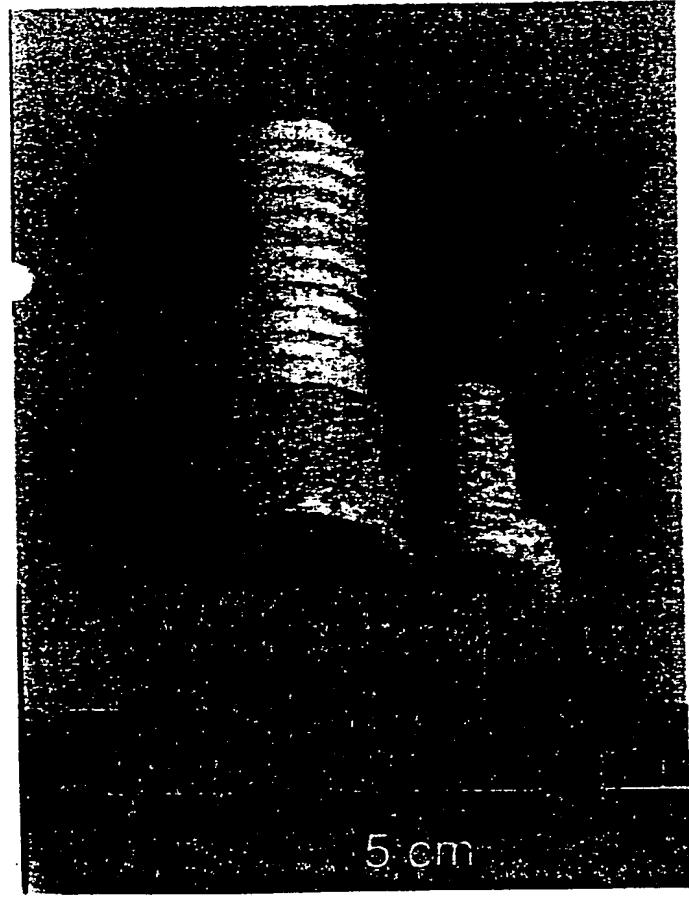
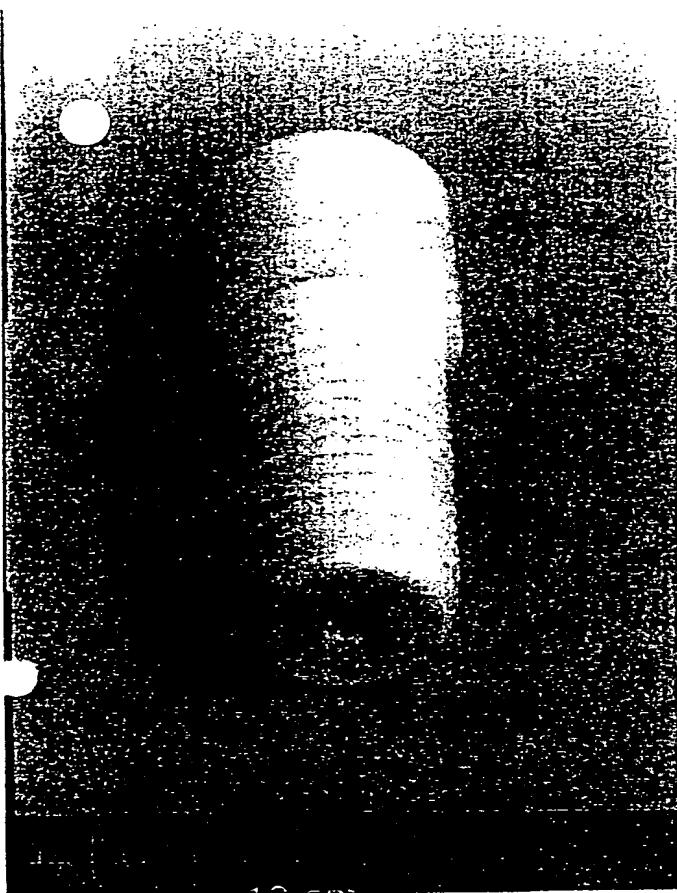


FIGURE 2 (cont'd)

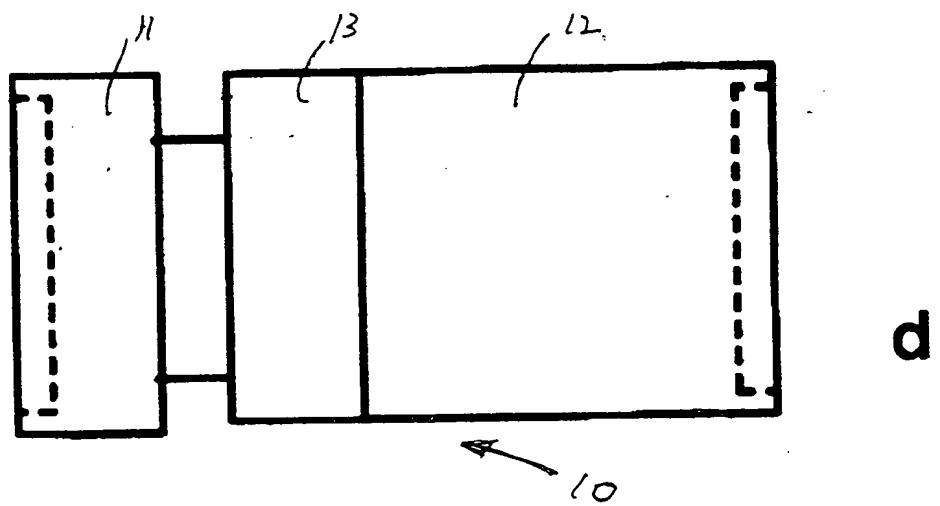
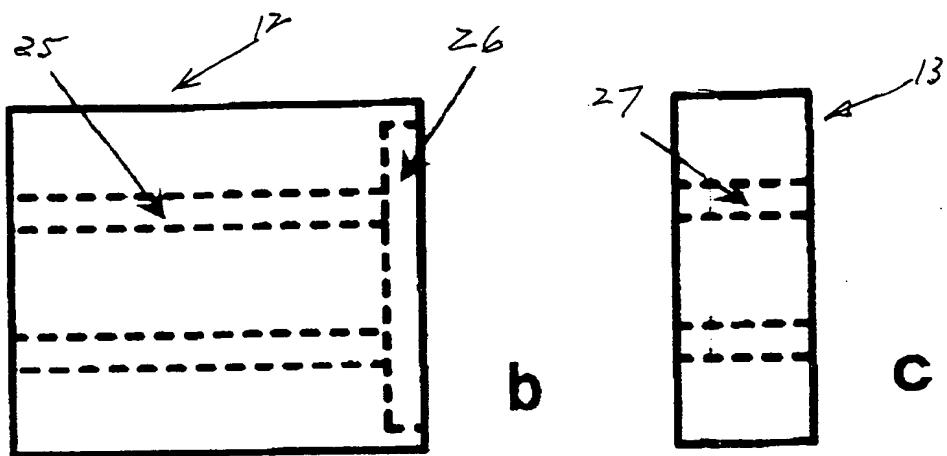
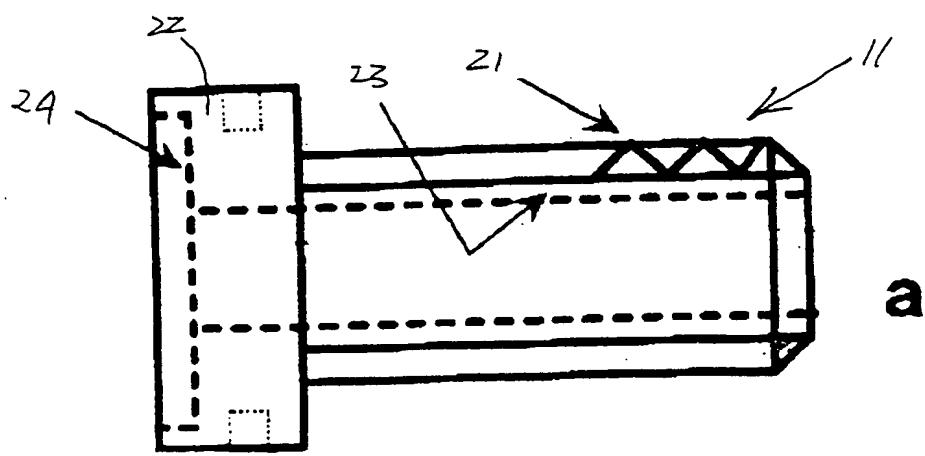


FIGURE 3

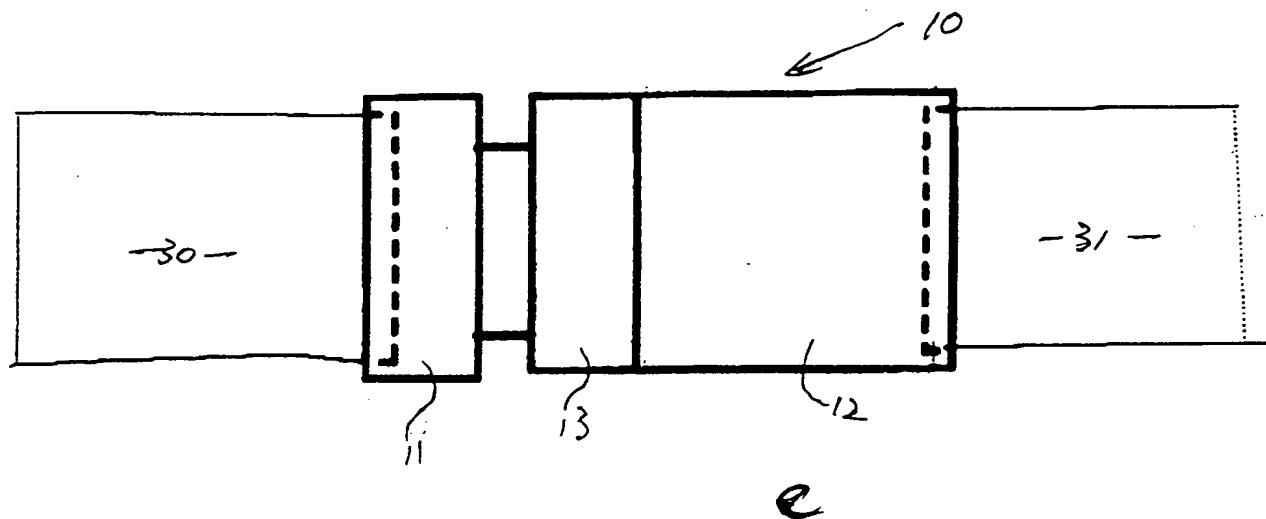


FIGURE 3 (cont'd)

THIS PAGE BLANK (USPTO)